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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,342	CALIGIURI ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003 and 20 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The supplementary amendment filed October 20, 2004 is acknowledged and has been entered. Claims 12-21 and 24-50 have been amended. Claims 51-62 have been added.

2. The supplementary amendment filed July 7, 2004 is again acknowledged; however, the amendment was not entered because the amendment was not compliant with the requirements set forth under 37 C.F.R. § 1.121.

3. The amendment filed September 15, 2003 is acknowledged. Applicant's remarks traversing the grounds of rejection set forth in the previous Office action are addressed herein; however, the amendment to the claims was not entered because the amendment was not compliant with the requirements set forth under 37 C.F.R. § 1.121.

4. Claims 12-62 are pending in the application and are currently under prosecution.

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. The following Office action contains NEW GROUNDS of rejection necessitated by amendment.

Grounds of Objection and Rejection Withdrawn

7. Unless specifically reiterated below, the amendment or arguments filed October 20, 2004 and September 15, 2003 have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 14, 2003.

Grounds of Objection and Rejection Maintained

Specification

8. The objection to the specification because of numerous references to "the CALGB 9661 Protocol" and citations therein is maintained.

The ground of this objection is set forth in section 6 of the previous Office action mailed March 14, 2003.

At page 22 of the amendment filed September 15, 2003, Applicant has traversed this ground of objection. Referring to the specification at page, 2, line 30, through page 3, line 4, Applicant has remarked, "the cited protocol is from a clinical trial, and this is the standard citation method for citing a clinical trial protocol" (page 22, paragraph 2).

In reply, the specification attempts to incorporate by reference the contents of a document that is not cited in a manner that identifies that document so that it might be considered. As explained in the previous Office action, it cannot be ascertained if, or by what means "the CALGB 9661 Protocol" might be acquired and considered. Moreover, the specification refers to citations apparently set forth in this document, which are not identified by any means other than by the reference numbers used in that document; so, the nature of the cited material, whether, for example, published or unpublished, cannot be ascertained.

Applicant has offered to submit a copy of the protocol. As it appears that the material that the specification attempts to incorporate by reference is essential material, because the document is not a U.S. patent, a U.S. patent application or a pending U.S. patent application, Applicant should amend the specification to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). See MPEP §§ 608.01(p) and 2163.07(b).

9. The objection to the specification because the use of improperly demarcated trademarks in this application is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Additional examples of improperly demarcated trademarks include LabCorp™ (page 5, line 5) and Benadryl™ (page 36, line 30).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Rejections - 35 USC § 112

10. The rejection of claims 25 and 31 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This is a new matter rejection; the ground of rejection is set forth in section 13 of the Office action mailed March 14, 2003.

At pages 23-25 of the amendment filed September 15, 2003, Applicant has traversed this ground of rejection, arguing that written support for the term "human form of a murine antibody", as presently recited in claims 25 and 31, can be found in the specification at page 23, line 26, through page 24, line 2; and page 24, line 7, through page 25, line 10. Furthermore, Applicant has asserted, as the specification discloses: "In practice, humanized antibodies are typically *human* [emphasis added] antibodies" (page 24, paragraph 3).

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The disclosure at page 23, line 26, through page 24, line 2 to which Applicant has referred appears to provide written support for a "human antibody", though not for a "human form of a murine antibody". A human antibody, even if it binds to the same antigen as a murine antibody, would not be described as a human form of a murine antibody. Furthermore, despite the disclosure at page 25, lines 6-10, humanized antibodies are not typically human antibodies; rather, humanized antibodies are chimeric antibodies comprising parts of a human antibody and parts of a different animal's antibody (e.g., a mouse antibody). Even *in practice*, humanized antibodies should not be regarded as typically human, because, for example, humanized antibodies are immunogenic in humans, whereas the human antibodies are not typically immunogenic. Applicant has argued that disclosures at pages 23-25 provide written support for the term "human form of a murine antibody"; however, to the contrary, the disclosures appear merely to provide support for a "humanized antibody" and a "human antibody". For example, at page 22, lines 11 and 12, the specification discloses: "Anti-HER2 antibodies of murine origin and their humanized and chimeric versions are suitable for use in the methods of the present invention." "Humanized antibodies", "chimeric antibodies", "human antibodies", and "murine antibodies" are common terms of art, which are readily understood; however, a "human form of a murine antibody" is not a common term of art. Moreover, neither a "humanized antibody" nor a "human antibody" would be understood to be the equivalent of "a human form of a murine antibody". Thus, the specification appears to provide written support for "a humanized or chimeric version of a murine antibody", not a "human form of a murine antibody".

In addition, Applicant has asserted that U.S. Patent No. 6,054,561 teaches "a human form of the murine antibody 520C9". However, the patent does not; rather, it teaches a *humanized* version of the murine antibody.

Again, this issue might be resolved if Applicants were to point to particular disclosures in the specification, including the claims, as originally filed, that are believed to provide the necessary written support.

11. The rejection of claims 12-27 and 29-62 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

This is a written description rejection; the ground of this rejection is set forth in section 14 of the Office action mailed March 14, 2003.

At pages 25-28, Applicant has traversed this ground of rejection, arguing "it is clear that the claimed variants of IL-2 have function similar to the native IL-2 polypeptide" (page 26, paragraph 2). Furthermore, since the variant of IL-2 has at least 70% identity "with the amino acid sequence for IL-2", Applicant has asserted that the written description provision set forth under 35 U.S.C. § 112, first paragraph, has been met by the supporting disclosure of the claimed invention.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, "Written Description" Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

Applicant has argued that the because the variants of IL-2 have at least 70% amino acid sequence identity with IL-2 and must be therapeutically effective, or have function similar to IL-2, the written description requirement is met. However, as noted previously, the amino acid sequence of IL-2 is not disclosed (Office action mailed March 14, 2003, page 6, paragraph 2); so, the comparison recited in the claims cannot be made. Nevertheless, there appears no correlation between any particularly identifying structural feature common to the members of the genus of IL-2 molecules and any particularly identifying functional feature that is shared by at least a substantial number of the members of the genus. Because the members of the genus do not necessarily

have the *same* function as "IL-2", but according to Applicant's remarks, are only required to have a *similar* function, the members of the genus vary structurally and functionally.

Applicant has argued that variants of IL-2 comprising an amino acid sequence that is at least 70% identical to "IL-2" can be immediately recognized or distinguished by virtue of their therapeutic effectiveness in practicing the claimed invention, however, the endpoint by which the therapeutic effectiveness is measured is not recited in the claims and IL-2 is a multifunctional protein; so unless, the variants are required to have or retain a specific function of IL-2, the members of the genus could not be immediately envisioned, recognized, or distinguished.

In *Colbert v. Lofdahl*, 21 USPQ2d, 1068, 1071 (BPAI 1992), it was concluded, "[i]t is not sufficient to define the recombinant molecule by its principal biological activity, e.g., having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property."

Furthermore, in deciding *The Reagents of the University of California v. Eli Lilly*, 43 USPQ2d 1398 (CA FC 1997), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of IL-2 molecules and variants thereof by only their common ability be therapeutically effective does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

Applicant has argued that given benefit of the supporting disclosure, the members of the genus of IL-2 and variants thereof can be distinguished by the positive therapeutic response observed after treating patients with these molecules; however, Applicant is again reminded that the written description provision of 35 USC § 112 is severable from its enablement provision; that is, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant has argued that clams 27-31 recite "human IL-2"; see amendment, page 26, paragraph 3. Actually, claim 27 recites, "wherein said IL-2 or variant thereof is recombinantly produced and said IL-2 is human IL-2"; so, because the variant of IL-2 is not necessarily "human", claims 27-31 are not necessarily directed to "human IL-2". Nevertheless, if one skilled in the art were given two molecules, one of which is "human" and the other not, the artisan could not readily distinguish one from the other, since the specification has not described any particularly identifying feature, structural or functional, that unambiguously identifies or distinguishes the human molecule from others. Moreover, the specification fails to define those features of a human molecule that uniquely define that molecule as a "human" molecule.

In this instance, the genus of IL-2 and variant thereof is exemplified by the disclosure of a single non-representative species, namely Proleukin™ (aldesleukin), which is a recombinant human IL-2 mutein; see, e.g., the specification at page 29, lines 2-10. The disclosure of this one species of molecule is not deemed representative because the specification has not defined the structural and functional features of Proleukin™ that uniquely describe the members of the genus of IL-2 and variants thereof, as a whole, such that one skilled in the art could immediately discern at least most of its members.

Applicant has asserted, "recitation of at least 70% identity at the amino acid level is a very predictable structure of the sequences encompassed by the claimed invention" (page 27, paragraph 3); however, the a preponderance of factual evidence of record

indicates that to the contrary, the skilled artisan cannot accurately and reliably predict whether a protein having as little as 70% amino acid sequence identity with another protein will have or retain any particular function of the latter.

Applicant has argued that "IL-2" is a very well known protein, as evidenced by their attachment at Appendix A of the amendment (paragraph bridging pages 27 and 28); however, in the very next paragraph, Applicant has stated, "the present invention specifically envisions variants derived from '[c]onservative substitutions, such as exchanging one amino acid with another having similar properties,' and that '[I]n constructing variants of the IL-2 polypeptide of interest, modifications are made such that variants continue to possess the desired activity'" (page 28, paragraph 2). Thus, while Proleukin™, for example, is a well-known IL-2 mutein, the claims are not limited to well known proteins, but rather are specifically directed to a genus of functionally and structurally disparate molecules that can be used with therapeutic effectiveness in practicing the claimed invention.

Again, Applicant is reminded: The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description" Requirement (*supra*) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). These guidelines further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession

of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

Finally, at page 28, paragraph 3 of the amendment, Applicant has asserted that U.S. Patent No. 5,772,997, which has been incorporated by reference into the disclosure of the instant application, teaches "a human form of 4D5". To the contrary, however, the patent does not teach "a human form" of the murine monoclonal antibody; rather, it teaches humanized versions of such antibodies can be made. Therefore, with regard to claims 25 and 31, because neither a "humanized antibody" nor a "human antibody" would be understood to be the equivalent of "a human form of a murine antibody", the description of this subject matter is too inadequate to reasonably convey to the skilled artisan that Applicant had possession of the claimed invention.

12. The rejection of claims 12-62 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a patient diagnosed with breast cancer that overexpresses HER2 comprising administering to the patient a therapeutically effective amount of Herceptin™ in combination with a therapeutically effective amount of Proleukin™, does not reasonably provide enablement for a method for treating a subject having a cancer that is characterized by overexpression of HER2 is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

This is a scope of enablement rejection; the ground of this rejection is set forth in section 15 of the Office action mailed March 14, 2003.

At pages 28-36 of the amendment filed September 15, 2003, Applicant has traversed this ground of rejection. In brief, Applicant has argued that the supporting

disclosure of the claimed invention would be sufficient to enable the skilled artisan to use the claimed invention without undue experimentation, since, for example, experimentation is allowed with regard to multiple embodiments of a disclosed invention as long as the experimentation is not undue and inoperative embodiments within the scope of the claim does not necessarily render a claim non-enabled.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), it has been determined that the amount of guidance, direction, and exemplification disclosed in the specification be insufficient to enable the skilled artisan to use the claimed invention without first performing undue experimentation.

As evidenced by the teachings of Skolnick et al. (of record), the art of protein chemistry is highly unpredictable; apart from disclosing the use of Proleukin™, the specification does not exemplify the use of any other member of the genus of IL-2 molecules and variants thereof to which the claims refer.

In re Fisher, 166 USPQ 18 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different biological and pharmacological activities.

Although the "variant of IL-2" has an amino acid sequence that is at least about 70% identical to the amino acid sequence of IL-2, the specification does not teach the amino acid sequence of IL-2.

Moreover, the specification fails to teach which amino acids of the amino acid sequence of human IL-2 can be replaced or deleted, or between which amino acids additional amino acids can be inserted, or by which other amino acids replacements can be made, so the variant retains the activity of human IL-2. Given that the skilled artisan

cannot predict which variants of human IL-2 will retain the function of Proleukin™ and, moreover, that the specification fails to provide sufficient guidance and direction necessary to enable the skilled artisan to make such functional variants of IL-2, the skilled artisan could not make and use at least a substantial number of members of the genus of IL-2 molecules to which the claims refer without having the need to perform additional, undue experimentation.

As noted previously, the claims encompass methods comprising administering to a subject an antibody that binds a non-extracellular domain of HER2. Applicant has remarked that the previous Office action fails to establish a *prima facie* case of the insufficiency of the disclosure to enable such embodiments; however, as previously noted, it appears that antibodies that bind to the intracellular domain HER2 are not disclosed in the specification. Moreover, the previous Office action clearly states, "the means by which such an antibody can be delivered to the tumor cells *in vivo* has not been addressed in the specification" (page 10, paragraph 3). Antibodies that bind the extracellular domain of the antigen displayed at the surface of cells are targeted selectively to those cells by virtue of the expression of the antigen; in contrast, antibodies that bind the intracellular domain of the antigen are not; accordingly, the previous Office action duly raises the question of how antibodies that do not bind the extracellular domain of HER2 can be used therapeutically, absent guidance and direction showing how antibodies that bind, for example, the intracellular domain can be delivered to the tumor cells *in vivo*.

The specification describes two species of anti-HER2 antibodies that bind the extracellular domain of HER2 with which it is asserted that the claimed invention can be practiced with a reasonable expectation of success. However, the prior art teaches that although an antibody binds HER2, the antibody is not necessarily capable of inhibiting the growth of cancer cells that express HER2 at the cell surface; see, e.g., Stancovski et al. and Lewis et al. (both of record). Applicant has argued that non-working embodiments in generic claims are permissible, which is true, so long that the claimed invention can be used without having to perform undue experimentation. The point of citing Stancovski et al. and Lewis et al. is to show that the skilled artisan cannot predict

which anti-HER2 antibodies can be used to treat cancer, since only certain antibodies can be used effectively to inhibit the growth of cancer cells. The specification has not provided the guidance and direction necessary to enable the skilled artisan to distinguish which anti-HER2 antibodies can or cannot be used effectively, but moreover, as evidenced by U.S. Patent No. 5,772,997A (of record), it appears only antibodies that bind a few particular epitopes of the extracellular domain of HER2 are capable of inhibiting the growth of tumor cells. Again, while the patent does not disclose anti-HER2 antibodies that promote the growth of breast cancer cells, as does Stancovski et al. and Lewis et al., the patent does disclose that the growth inhibitory properties of monoclonal antibody 4D5 are somewhat unique because other anti-HER2 antibodies were found to inhibit the growth of the cells to a lesser extent, or not at all.

The specification discloses that only patients having breast cancer responded positively to treatment with exemplified embodiment of the invention. Again, Applicant has argued that non-working embodiments in generic claims are permissible, but the point of citing Lewis et al. (of record) is to show that despite over-expressing HER2, not all types of cancer cells are inhibited by monoclonal antibody 4D5. Again, Lewis et al. teaches the monoclonal antibody does not affect the proliferation of gastric and colon cancer cells, even though the cells express an amount of HER2 that is equivalent to the amount expressed by breast cancer cells that are sensitive to the effects of treatment with the antibody. Given this fact, the skilled artisan could not reasonably expect to use the claimed invention to treat types of cancer, other than breast cancers overexpressing HER2, without first determining whether the antibody is capable of inhibiting the growth of the other types of cancer; since Lewis et al. shows that the skilled artisan cannot accurately and reliably predict which types of cancer can or cannot be treated on the basis of the level of expression of HER2, the determination can only be made empirically and therefore additional undue experimentation would be required before the claimed invention could be used.

Regarding any greater effectiveness of the combination of Herceptin™ (i.e., Trastuzumab, a recombinant humanized version of murine monoclonal antibody 4D5)

and Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein), it appears from Applicant's disclosure that it would depend upon the ability of the antibody to mediate antibody-dependent cell cytotoxicity (ADCC); otherwise, the presence of IL-2-activated effector cells would not be expected to enhance the antiproliferative, i.e., therapeutic, effect of an anti-HER2 antibody. Applicant has argued that it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works, which is true. Nevertheless, as previously explained, the recombinant humanized version of the murine monoclonal antibody 4D5, namely Herceptin™ has been shown to mediate ADCC; and the conventional wisdom in the art is that it is by this mechanism, albeit not by this mechanism alone, that Herceptin™ mediates its growth inhibitory effects upon tumors in patients. However, Lewis et al. (of record) teaches that the *murine* monoclonal antibody does not mediate ADCC, and is further incapable of fixing complement to mediate complement-mediated cell cytotoxicity. Thus, if by no other mechanism Herceptin™ achieves its effectiveness, the teachings of Lewis et al. suggest that because the murine antibody does not mediate ADCC, the murine antibody cannot be used before first determining whether the murine antibody can effectively inhibit the growth of cancer cells in patients by some other mechanism and whether administering IL-2 in combination with the antibody will enhance or perturb this mechanism. Stancovski et al. (of record) discloses that of mouse anti-HER2 antibodies found to inhibit the growth of tumor cells, *none were found to mediate ADCC*, suggesting that the mechanism by which mouse anti-HER2 antibodies typically affect the proliferation of cells is not effector cell-dependent, and further suggesting that monoclonal antibody 520C9 is unusual in its ability to mediate ADCC. As Applicant has remarked, it is not necessary that the inventor understand how or why the combination of Herceptin™ and Proleukin™ is effective, but the claims are not presently limited to the use of a combination that is known to be effective. Given the teachings of Lewis et al. and Stancovski et al., it appears that murine anti-HER2 antibodies will not generally be found to be the therapeutic equivalent of Herceptin™, since, for example, murine monoclonal antibody 4D5 lacks the ability to mediate ADCC; accordingly, the amount of

guidance, direction, and exemplification is not reasonably commensurate in scope with the breadth of the subject matter claimed. Because the art is unpredictable, undue experimentation would have to be performed before the claimed invention could be used.

As set forth previously, even though monoclonal antibody 520C9 is capable of mediating ADCC, the embodiment in which the monoclonal antibody is used has not been exemplified. The art teaches that a bispecific recombinant antibody comprising an antigen-binding fragment of the monoclonal antibody can be used to inhibit the growth of tumor cells. The art teaches that an immunotoxin comprising the antibody can be used to inhibit the growth of tumor cells, but the art does not teach that the monoclonal antibody itself, or any fragment thereof, is capable of effectively inhibiting the growth of tumor cells *in vivo*. In fact, Keler et al. (of record) demonstrates the $F(ab')_2$ fragment of monoclonal antibody 520C9 is relatively incapable of mediating ADCC compared to MDX-H210, a recombinant bispecific antibody comprising a Fab' fragment of 520C9.

In conclusion, the various factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. After careful consideration of these factors, a preponderance of factual evidence of record indicates that the amount of guidance, direction, and exemplification disclosed in the specification would not be sufficient to enable the skilled artisan to use the claimed invention without an undue experimentation.

For clarity, although the previous Office action further states that it does not appear that the specification provides guidance as to when the different embodiments should, or should not be practiced, since the specification does not teach or exemplify how the most appropriate doses, or ranges thereof should be selected, or upon what criteria, upon reconsideration in light of Applicant's arguments, achieving the optimal

schedule and dosing regimens to be used in treating a patient diagnosed with breast cancer by administering to the patient therapeutically effective amounts of both Herceptin™ and Proleukin™ to achieve clinically relevant antitumor effects would not fall into the realm of undue experimentation.

13. The rejection of claims 25, 31, 52, 55, 58, and 61 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This is an enablement rejection; the ground of rejection is set forth in section 16 of the Office action mailed march 14, 2003.

At pages 36-38, Applicant has traversed this ground of rejection arguing that no deposit should be required of biologic materials that can be obtained from publicly available material with only routine experimentation and a reliable screening test. Applicant has asserted that the monoclonal antibodies to which the claims are specifically can be reproduced by, for example, the well-known methodology first described by Kohler et al. Furthermore, Applicant has stated that hybridomas producing the monoclonal antibodies 4D5 and 520C9 have been deposited under ATCC Accession Nos. CRL 10463 and HB8696, respectively, in fulfillment of the patentability requirements of U.S. Patent Nos. 5,677,171 and 6,054,561, respectively.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has argued that monoclonal antibodies 4D5 and 520C9 could be acquired or reproduced without undue experimentation and more notably without need to access deposited biological materials, such as the hybridoma producing the antibodies; however, reproducing these monoclonal antibodies by the methodology of Kohler et al., for example, is unpredictable, uncertain, or virtually an impossibility because of polymorphism and the inexact, random nature of the recombination events that produce alleles encoding antibodies. While one could produce an antibody that

binds to the same antigen and has some or most of the identifying characteristics of either of these antibodies, the skilled artisan would not reasonably expect to reproduce the monoclonal antibodies to which the claims are specifically directed; thus, the reason that deposits of such specific biological materials are required. See MPEP § 2400. Without a publicly available deposit of a specific biological material or a cell line producing such, one skilled in the art could not be assured of the ability to practice the invention as claimed.

Provided one has assess to the hybridoma producing said antibodies, MPEP § 2401.01 states to avoid the need for a deposit, biological materials must be known and readily available – *neither concept alone suffices*.

Although Applicant has remarked that deposits of the hybridoma cell lines producing both monoclonal antibodies have been made, Applicant has failed to make of record any of the facts and circumstances surrounding the access to the biological materials from said depository. The fact that Applicant and other members of the public were able to obtain the materials in question from a given depository and that reference to the material or a deposit thereof has been made in various publications prior to and after the filing date of the application does not establish that upon issuance of a patent on this application that such material would continue to be accessible to the public.

Applicant's remarks suggest that U.S. Patent Nos. 5,677,171 and 6,054,561 refer to deposits under ATCC Accession Nos. CRL 10463 and HB8696, respectively, of the hybridoma cell lines producing these monoclonal antibodies. However, the applications (i.e., 08/286,303 and 08/483,749) upon which these patents issued cannot be attained for review of the record, as the applications are presently located with the Board of Patent Appeals and Interferences. The applications must be reviewed to determine whether the record includes a statement by an attorney of record having authority and control over the conditions of the stated deposit that the deposit had been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits were to be irrevocably removed upon the grant of a patent on the application, and that the deposit would be replaced if viable samples cannot be dispensed by the depository and whether there was a provision of

assurances that all restrictions imposed by the depositor on the availability to the public of the deposited material were to be irrevocably removed upon the granting of the patent.

Nonetheless, MPEP § 2404.01 states:

> The mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless the deposit was made under conditions that are consistent with those specified in these rules, including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the applicant upon the granting of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990).

Applicant has not provided the required assurance that said depository would allow unlimited access to the material upon the issue of a patent upon this application. In the absence of evidence that the hybridoma producing monoclonal antibodies 4D5 and 520C9 are readily available to the public and that all restrictions imposed by the depositor, or by other investigators on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, the rejection is properly maintained.

If Applicant can establish that hybridomas producing monoclonal antibodies 4D5 and 520C9 are known and readily available, the Office will accept the showing. However, it should be noted that Applicant will take the risk that the material may cease to be known and readily available; and such a defect cannot be cured by reissue after the grant of a patent.

Having not resolved this issue, Applicant is again advised that a suitable deposit would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph (see 37 C.F.R. 1.801-1.809).

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an

International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by Applicant or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature must be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth under 37 CFR §§ 1.801-1.809 have been met.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

Claim Rejections - 35 USC §§ 102 and/or 103

14. The rejections of claims 12-19, 24, 26-28, 30, 32-40, 42-47, 51-62 under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over US Patent Nos. 4,863,726 A or 4,894,227 A are maintained.

These grounds of this rejection are set forth in section 20 of the Office action mailed March 14, 2003.

At page 38 of the amendment filed September 15, 2003, Applicant has traversed this ground of rejection arguing that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. Then, at pages 38 and 39, Applicant has further traversed this ground of rejection arguing, as an initial matter, that one can scientifically extrapolate in any number of directions from a given disclosure and that there is no legal basis for rejecting

claims on grounds of extrapolation. In addition, Applicant has asserted that the impermissible hindsight reasoning has been used.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 12-19, 24, 26-28, 30, 32-40, 42-47, 51-62 are rejected as being anticipated by *or, in the alternative, obvious over the prior art*. Applicant has argued that the prior art does not teach that a therapeutically effective dose of IL-2 is in the range of about 05 to about 4.0 mIU/m^2 or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg. Nevertheless, the prior art discloses exemplary dosing and scheduling and teaches that the dosage and scheduling must be adjusted to obtain efficacious results and in particular, to achieve some tumor reduction or augmentation of LAK activity. Moreover, the prior art teaches that combinations of drugs are administered in an attempt to obtain a synergistic cytotoxic effect on most cancers, such that the administration of the combination of agents inhibits tumor growth to a greater extent than the administration of either agent alone. The prior art further discloses that dose and dosage regimen will depend on whether IL-2 and antibody are being administered separately or as a mixture, the type of antibody, the type of cancer, the subject, and the subject's history. If multiple doses are employed, the prior art teaches the frequency of administration will depend, for example, on the type of component, the type of cancer, the dosage amounts, the subject, etc. For some types of cancers, the prior art teaches daily administration may be effective, whereas for other types of cancer, administration every other day or every third day may be effective. In any event, the prior art teaches the practitioner will be able to ascertain from clinical trials which route of administration and frequency of administration are most effective in humans. Therefore, if the prior art is not clearly anticipatory of the claimed invention, particularly since the prior art does not explicitly teach that a therapeutically effective dose of IL-2 is the range of about 0.5 to about 4.0 mIU/m^2 or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg, any necessary or appropriate modification of the methods

disclosed by the prior art, which would be amply guided by the supporting disclosures, would have been obvious to the ordinarily skilled artisan at the time of the invention.

Applicant has remarked that one can scientifically extrapolate in any number of directions from a given disclosure and that there is no legal basis for rejecting claims on grounds of extrapolation. This remark appears directed at the statement in the rejection at page 18, paragraph 1, which reads, "[t]he skilled artisan could extrapolate, if need be, as '726 and '227 disclose that various modifications of the method will be apparent to those skilled in the art, so that the disclosures provide sufficient guidance to enable the skilled artisan to practice the invention in cases where the subject is a human". This, the Office action further states, is evidenced by, for example, claim 11 of US Patent No. 4,863,726 A. The term "extrapolate" should have been given only its plain meaning; e.g., to estimate by projecting known data. The prior art exemplifies the methods disclosed therein by disclosing the results of experiments in which the subjects treated were mice; simply because mice are much smaller animals than humans, the artisan would know to extrapolate the data shown, or to estimate the correct dosages, for example, that should be administered when using the disclosed methods to treat breast cancer in human subjects. Nonetheless, it is aptly noted that the claims are not limited to methods for treating cancer in a human subject and broadly but reasonably encompasses methods for treating cancer in mice and other animals. If the subject were a mouse, there would be no need to alter the exemplified methodology disclosed by the prior art.

Not to appear remiss, in response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

15. The rejections of claims 12-62 under 35 U.S.C. 103(a) as being unpatentable over US Patent Nos. 4,863,726-A or 4,894,227-A in view of Hank et al. (*Cancer Research* 1990; **50**: 5234-5239) and Keler et al. (*Cancer Research* 1997; **57**: 4008-4014), or Silwkowski et al. (*Seminars in Oncology* 1999; **26**: 60-70) and Lewis et al. (*Cancer Immunology & Immunotherapy* 1993; **37**: 255-263), and in further view of Meropol et al. (*Cancer Immunology & Immunotherapy* 1998; **46**: 318-326) are maintained.

These grounds of this rejection are set forth in section 21 of the Office action mailed March 14, 2003.

At pages 39-44, Applicant has traversed this ground of rejection. Briefly, Applicant has argued that the Examiner is attempting to point to a combination of all of the references cited, rather than to specific combinations. Applicant has remarked that the prior art does not expressly teach the dosing and scheduling regimens recited in the claims. Applicant has contended that the requisite motivation to combine the teachings of the cited references is lacking; or where the motivation to combine the teachings may be present in the references, the combination of references fails to teach all the limitations of the claimed invention. Furthermore, Applicant has further contended that impermissible hindsight has been used in constructing the rejection. Finally, Applicant has asserted that at best, the combination of references would have merely provided motivation to try and that the ordinarily skilled artisan could not therefore have had a reasonable expectation of success.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Applicant has stated that the rejection does not point to specific combinations of references. However, it is believed that the rejection unambiguously states that claims 12-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 4,863,726 A in view of Hank et al. and Keler et al., and in further view of Meropol et al; or alternatively, over US Patent No. 4,894,227 A in view of Hank et al. and Keler et al., and in further view of Meropol et al.; or alternatively, over US Patent No. 4,863,726 A in view of Silwkowski et al. and Lewis et al., and in further view of Meropol et al; or

alternatively, over US Patent No. 4,894,227 A in view of Silwkowski et al. and Lewis et al., and in further view of Meropol et al. Thus, for sake of brevity, four separate grounds of rejection have been set forth in section 20 of the Office action.

Regarding each separate ground of rejection, the primary reference (either US Patent No. 4,894,227 A or US Patent No. 4,863,726 A) teaches that combining two treatment modalities, namely a therapeutically effective amount of Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein) and a therapeutically effective amount of anti-HER2 antibody 520C9 is effective to treat breast cancer in a subject. Although the primary reference does not expressly teach the recited dosages and schedules, the prior art discloses exemplary dosing and scheduling and teaches that the dosage and scheduling must be adjusted to obtain efficacious results and in particular, to achieve some tumor reduction or augmentation of LAK activity. Moreover, the prior art teaches that combinations of drugs are administered in an attempt to obtain a synergistic cytotoxic effect on most cancers, such that the administration of the combination of agents inhibits tumor growth to a greater extent than the administration of either agent alone. The prior art further discloses that dose and dosage regimen will depend on whether IL-2 and antibody are being administered separately or as a mixture, the type of antibody, the type of cancer, the subject, and the subject's history. If multiple doses are employed, the prior art teaches the frequency of administration will depend, for example, on the type of component, the type of cancer, the dosage amounts, the subject, etc. For some types of cancers, the prior art teaches daily administration may be effective, whereas for other types of cancer, administration every other day or every third day may be effective. In any event, the prior art teaches the practitioner will be able to ascertain from clinical trials which route of administration and frequency of administration are most effective in humans. Therefore, if the prior art is not clearly anticipatory of the claimed invention, particularly since the prior art does not explicitly teach that a therapeutically effective dose of IL-2 is the range of about 0.5 to about 4.0 mIU/m^2 or that a therapeutically effective dose of the antibody is in the range of about 1.0 to about 10.0 mg/kg, any necessary or appropriate modification of the methods

disclosed by the prior art, which would be amply guided by the supporting disclosures, would have been obvious to the ordinarily skilled artisan at the time of the invention.

The primary reference, however, does not expressly teach or suggest that the antibody is a recombinant chimeric or humanized antibody. Nevertheless, regarding each separate ground of rejection, one, all, or the combination of secondary references teaches or suggests the antibody is a recombinant chimeric or humanized version of an anti-HER2 monoclonal antibody.

As further noted in the rejection set forth in the previous Office action, the primary reference also does not teach the anti-HER2 antibody 4D5; while both Silwkowski et al. and Lewis et al. teach the monoclonal antibody or humanized versions thereof, neither Hank et al. nor Keler et al. teach this specific antibody. However, since none of claims are limited to one or the other antibody, as all claims recite both antibodies in the alternative, all claims are properly included in each ground of rejection.

The primary reference does not teach a treatment regimen comprising intermediate-dose IL-2 pulsing; nevertheless, Meropol et al. teaches such a treatment regimen.

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to Applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the Applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to Applicant's argument that there is no suggestion to combine the references, the Examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Concerning the motivation to combine the teachings of either of the primary references, i.e., US Patent No. 4,894,227 A or US Patent No. 4,863,726 A, Hank et al., and Keler et al., Hank et al. teaches enhanced LAK effector cell-mediated ADCC against tumor cells in the presence of tumor-specific monoclonal antibodies after treatments with the cytokine IL-2 and suggests combining IL-2 and tumor-specific monoclonal antibody in clinical treatment of cancer; whereas Keler et al. teaches a bispecific antibody comprising one arm that binds HER2 that selectively recruits effector cells that mediate ADCC to the tumor and further suggests that the therapeutic potential of bispecific antibody is enhanced in combination with cytokines. Again, the primary reference teaches the combination of IL-2 and monoclonal antibody 520C9 is effective to treat breast cancer; in addition, as previously noted, the primary reference also teaches that combining effective amounts of these therapeutic agents augments LAK effector cell activity, promoting the achieved tumor reductions. Therefore, because Keler et al. teaches a bispecific antibody that comprises the binding domain of monoclonal antibody 520C9 and another arm that binds a receptor molecule at the surface of effector cells, which recruits effector cells to the tumor, suggesting also that the *in vivo* cytotoxic potential of this bispecific antibody is enhanced in combination with cytokine therapy, and moreover because Hank et al. teaches that IL-2 enhances ADCC of tumor cells mediated by such effector cells, the suggestion to combine the teachings is found in the references themselves.

Concerning the motivation to combine the teachings of either of the primary references, i.e., US Patent No. 4,894,227 A or US Patent No. 4,863,726 A, Silwkowski et al., and Lewis et al., both secondary references teach chimeric versions of

monoclonal antibody 4D5. The primary reference only teaches monoclonal antibody 520C9. Silwkowski et al., for example, teaches Herceptin™, a humanized version of the antibody, which Silwkowski et al. discloses is also used effectively to treat breast cancer. In addition, both references teach the antibodies were produced to provide the potential for ADCC; Silwkowski et al. teaches Herceptin™ has been found to very effectively mediate ADCC against HER2-overexpressing tumor cells by IL-2 treated effector cells. Therefore, the suggestion to combine the teachings is found in the references themselves.

Again, the primary reference teaches teaches that combining two treatment modalities, namely a therapeutically effective amount of Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein) and a therapeutically effective amount of anti-HER2 antibody 520C9 is effective to treat breast cancer in a subject. However, neither the primary reference nor either of the secondary references teaches a regimen comprising intermediate-dose IL-2 pulsing. Meropol et al. teaches that the inclusion of intermediate-dose IL-2 pulsing is well tolerated on an out-patient basis and overcomes the limitations of continuous low-dose IL-2 infusions, because an IL-2 concentration in the patient can be achieved, which is sufficient to engage a significant portion of the IL-2Rβγ complexes present on an expanded population of natural killer cells to better maintain an activated state. Meropol et al. discloses the maximum tolerated pulse dose of IL-2 was found to be 15 MIU/m^2; and the highest, best-tolerated dose was found to be 12 MIU/m^2. Meropol et al. teaches that a three-day pulse can be used effectively after an initial low-dose cycle of about 1.25 MIU/m^2 and can be repeated about every two weeks. Accordingly, the suggestion to combine the teachings is found in the references themselves.

Finally, Applicant has asserted that at best, the combination of references would have merely provided motivation to try and that the ordinarily skilled artisan could not therefore have had a reasonable expectation of success. Again, the primary reference teaches that combining two treatment modalities, namely a therapeutically effective amount of Proleukin™ (i.e., Aldesleukin, a recombinant human IL-2 mutein) and a

therapeutically effective amount of anti-HER2 antibody 520C9 is effective to treat breast cancer in a subject. Applicant has not actually stated why one ordinarily skilled in the art at the time of the invention would not have had a reasonable expectation of successfully using the claimed invention, but both Lewis et al. and Silwkowski et al. teach another anti-HER2 antibody that is also used effectively to treat breast cancer; so it appears that the murine monoclonal antibody 520C9 could be substituted for the chimeric or humanized versions of monoclonal antibody 4D5 and still one would have had a reasonable expectation of success in treating breast cancer. Keler et al. teaches a bispecific antibody comprising an arm comprising the antigen-binding domain of monoclonal antibody 520C9, which recruits effector cells to tumor cells expressing HER2, and therefore Keler et al. suggests that the bispecific antibody be used to treat malignancies that overexpress HER2. So, in view of Hank et al., contrary to Applicant's assertion, it appears that one ordinarily skilled in the art would have had a reasonable expectation of success in using the bispecific antibody of Keler et al. in lieu of the murine monoclonal antibody disclosed by the primary reference.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

16. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

17. Claims 12-27 and 29-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-27 and 29-62 are indefinite because the claims use of the designation "IL-2" or "human IL-2" as the sole means of identifying the polypeptide to which said variant of "said IL-2" has at least 70% amino acid sequence identity. The use of such a designation alone to identify a particular polypeptide renders the claims indefinite because same designation may be used to define completely distinct polypeptides. At page 14, lines 11-14, for example, the specification teaches the need to know the amino

acid sequence that serves as the reference or basis for comparison. In this instance, however, the amino acid sequences of "IL-2" and, in the case of claim 27, 53, 56, and 62, "human IL-2" are not disclosed. So, because a comparison cannot be made without a disclosure of the specific reference to which said comparison is made, the metes and bounds of the subject matter that Applicant regards as the invention cannot be determined.

Conclusion

18. No claims are allowed.

19. As first noted in section 8 of the previous Office action mailed March 14, 2003, Applicant is again advised that should claims 18 and 38-40 be found allowable, claims 43-46 will be objected to under 37 CFR § 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
February 16, 2005

LARRY R. HELMS, PH.D
PRIMARY EXAMINER